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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,554 06/28/2001		Anna Edman Orlefors	HO-P0221US0	4792
26271	7590 10/29/2004		EXAM	INER
FULBRIGHT & JAWORSKI, LLP 1301 MCKINNEY SUITE 5100 HOUSTON, TX 77010-3095			SAKELARIS, SALLY A	
			ART UNIT	PAPER NUMBER
			1634	
			DATE MAILED: 10/29/2004	1

Please find below and/or attached an Office communication concerning this application or proceeding.

	Application No.	Applicant(s)			
	09/869,554 ORLEFORS ET AL.				
Office Action Summary	Examiner	Art Unit			
	Sally A Sakelaris	1634			
The MAILING DATE of this communication appeared for Reply	opears on the cover sheet wi	th the correspondence address			
A SHORTENED STATUTORY PERIOD FOR REP THE MAILING DATE OF THIS COMMUNICATION - Extensions of time may be available under the provisions of 37 CFR 1 after SIX (6) MONTHS from the mailing date of this communication. - If the period for reply specified above is less than thirty (30) days, a re - If NO period for reply is specified above, the maximum statutory perior - Failure to reply within the set or extended period for reply will, by statu Any reply received by the Office later than three months after the mailing earned patent term adjustment. See 37 CFR 1.704(b).	136(a). In no event, however, may a reply within the statutory minimum of thirt d will apply and will expire SIX (6) MON to Cause the application to become AB.	eply be timely filed y (30) days will be considered timely. THS from the mailing date of this communication.			
Status					
1) Responsive to communication(s) filed on 01					
	is action is non-final.				
3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is					
closed in accordance with the practice under	Ex parte Quayle, 1935 C.D.	. 11, 453 O.G. 213.			
Disposition of Claims					
4)	ected.				
Application Papers					
9) The specification is objected to by the Examiner.					
10) The drawing(s) filed on is/are: a) accepted or b) objected to by the Examiner.					
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a). Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).					
11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.					
Priority under 35 U.S.C. § 119					
12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). a) All b) Some col None of: 1. Certified copies of the priority documents have been received. 2. Certified copies of the priority documents have been received in Application No 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)). * See the attached detailed Office action for a list of the certified copies not received.					
Attachment(s) 1) Notice of References Cited (PTO-892) 2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date	Paper No(s)	mmary (PTO-413) /Mail Date ormal Patent Application (PTO-152)			

Art Unit: 1634

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 10/1/2004 have been entered.

Claims 2, 4, 6, 19, 25, 29, and 32-34 have been amended, claims 1, 3, 5, 7-11, 13-15, and 17-18, have been canceled, and claims 41-56 have been added. Claims 2, 4, 6, 12, 16, and 19-56 are now pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. All rejections not reiterated herein are hereby withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Art Unit: 1634

2. Claims 2, 20, 21, 32, 35, 36 and new claim 42 are rejected under 35 U.S.C. 102(b) as being unpatentable over Ronaghi et al.(Anal. Biochemistry, 1996).

Interpreting claim 2's recitation of a "microfluidic device" to mean any device which is suitable to operate with liquids on a microliter scale, Ronaghi et al. teaches the methods of such a device(for example the capillary embodiment on page 88 bottom right).

With respect to claim 2, Ronaghi et al. teach a method of identifying the sequence of a portion of sample DNA comprising the steps of:

- (i) forming immobilized DNA comprising of one strand of sample DNA and one strand of primer DNA on one or more reaction areas in a microchannel structure of a microfluidic device(Pg. 85, bottom right). Incubating the nucleic acid sample with about 0.8 pmol primer, DNA polymerase, and a deoxynucleotide triphosphate(Page 88, Fig. 5).
- (ii) adding reagents including deoxynucleotide or deoxynucleotide analogue and DNA polymerase and moving said reagents within said microchannel structure to each of said one or more reaction areas so that extension of primer occurs as a result from complementarity of the added deoxynucleotide or deoxynucleotide analogue with the strand of sample DNA that is part of the immobilized double stranded DNA(Page 85- 86)
- (iii) detecting whether or not the deoxynucleotide or deoxynucleotide analogue added in step (ii) is added to the primer DNA in said one or more reaction areas;(Page 86).
- (iv) removing excess of said deoxynucleotide or deoxynucleotide analogue from said from one or more reaction areas; is taught throughout the Ronaghi reference in their teachings in Figure 1 and later on page 87 as they wash the beads on which the deoxynucleotides are

Art Unit: 1634

immobilized, the reference further teaches the loss of these excess, unincorporated, deoxynucleotides following the wash steps on page 87.

- (v) repeating steps (ii)-(iv) with different deoxynucleotides or deoxynucleotide analogues is taught by Ronaghi in Figure 1 and in the text of Page 87 in their teaching that "the sequencing procedures were repeated several times".
- (vi) identifying said sequence from the results of the above previous steps is obviously then taught in the reference's sequencing previously alluded to in (v) and furthermore that "the obtained sequence was confirmed by semiautomated solid-phase Sanger sequencing" (Pg. 87, see figure 5).

With regard to claim 20, Ronaghi et al. teaches the above method wherein the detecting step (iii) measures the release of pyrophosphate(Page 85).

With regard to claim 21, Ronaghi et al further teach the method wherein the pyrophosphate release is detected by light emitted from a luciferin luciferase reaction(Fig. 1, Pg. 85).

With regard to new claim 32, Ronaghi et al. further teaches the method of claim 2 wherein step (iv) is washing said one or more reaction areas to remove excess of said deoxynucleotide or deoxynucleotide analogue in their teaching on the left side of page 85 of "washing of the immobilized DNA fragments between each nucleotide addition was performed" (Ronaghi pg. 85). Additionally the reference teaches in the abstract that the "parallel processing of many samples in an automated manner is discussed".

With regard to claims 35 and 36, the reference anticipates the limitations of the method of claim 2 and claim 35 wherein the amount of DNA sample is in the range of about 1 femtomole to

Art Unit: 1634

about 200 pmole and also about 0.1 pmol to about 200 pmol in their teaching on page 85 of "one picomole of the immobilized DNA fragment" being used in the sequencing reaction.

With regard to new claim 42, the reference anticipates the limitations of the method of claim 2 and claim 42 wherein said immobilized DNA is immobilized to a bead in their teaching on page 85 of "the biotinylated PCR products were immobilized onto streptavidin-coated super paramagnetic beads Dynabeads M280-Streptavidin or M450-streptavidin" (left hand side), which were later used for sequencing.

Response to Arguments:

Applicant's arguments filed 10/1/2004 have been fully considered but they are not persuasive. While applicant argues that Ronaghi's teaching stating "a flow system, with small volumes, high speed and low cost" has been erroneously construed by the examiner as the reference "does not teach or suggest forming immobilized DNA in one or more reaction areas in a microchannel of a microfluidic device, and sequentially adding reagents to the microchannel, moving the reagents to the reaction areas, detecting if addition to the primer has occurred, removing reagents, and then repeating the steps with another deoxynucleotide/deoxynucleotide analogue" (Response of 10/1/04). The response goes on to assert that the Ronaghi et al. reference merely mentions a "flow system", it does not teach how to perform Ronaghi's method in any type of flow system and further that there is no indication that the flow system as stated in Ronaghi et al. would move reagents to a reaction area in a microchannel structure of a microfluidic device as stated in the present specification. However, applicant in reminded that limitations of the specification cannot be read into the claims and the claims have to be examined as broadly as they could be read. Limitations in applicant's arguments, specification etc cannot

Art Unit: 1634

be read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, without a requirement in the claims for the exact device that is used in this method that applicant is arguing, the art will be applied as broadly as the claims are written. The courts have stated that claims must be given their broadest reasonable interpretation consistent with the specification In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); In re Prater, 415 F.2d 1393, 1404-05, 162 USPO 541, 550-551 (CCPA 1969); and In re Zletz. 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (see MPEP 2111). Applicant is pointed to page 88 of the Ronaghi reference and their teaching of their immobilization of the DNA template in a capillary and their further characterization of such a system as "a flow system, with small volumes, high speed", which meets applicant's own standard of a characteristic of a microfluidic device. In addition applicant argues that their limitation requiring that fluids are moved within the microchannel structure is not taught by Ronaghi et al. Although this limitation is acknowledged, it does not make the claim free of the cited prior art. Again, applicant is pointed to the "flow system" (pg. 88) that is described in the Ronaghi reference that anticipates this new limitation of moving in the microchannel structure. While applicant's arguments regarding the inherency issue are acknowledged, the examiner maintains her previous position. Applicant is arguing limitations of their claims that lack an explicit definition in the specification and as a result are open to interpretation in their broadest sense.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 2, 4, 6, 12, 16, 19-31, 33, 34, 37-40, and new claims 41-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ronaghi et al.(Anal. Biochemistry, 1996) in view of Mian et al.(US Patent 6,319,469 B1).

Interpreting claim 2's recitation of a "microfluidic device" to mean any device which is suitable to operate with liquids on a microliter scale, Ronaghi et al. teaches the methods of such a device(for example the capillary embodiment on page 88 bottom right).

With respect to claim 2, Ronaghi et al. teach a method of identifying the sequence of a portion of sample DNA comprising the steps of:

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- (ii) adding reagents including deoxynucleotide or deoxynucleotide analogue and DNA polymerase and moving said reagents within said microchannel structure to each of said one or more reaction areas so that extension of primer occurs as a result from complementarity of the added deoxynucleotide or deoxynucleotide analogue with the strand of sample DNA that is part of the immobilized double stranded DNA(Page 85- 86)
- (iii) detecting whether or not the deoxynucleotide or deoxynucleotide analogue added in step (ii) is added to the primer DNA in said one or more reaction areas;(Page 86).

Art Unit: 1634

- (iv) removing excess of said deoxynucleotide or deoxynucleotide analogue from said from one or more reaction areas; is taught throughout the Ronaghi reference in their teachings in Figure 1 and later on page 87 as they wash the beads on which the deoxynucleotides are immobilized, the reference further teaches the loss of these excess, unincorporated, deoxynucleotides following the wash steps on page 87.
- (v) repeating steps (ii)-(iv) with different deoxynucleotides or deoxynucleotide analogues is taught by Ronaghi in Figure 1 and in the text of Page 87 in their teaching that "the sequencing procedures were repeated several times".
- (vi) identifying said sequence from the results of the above previous steps is obviously then taught in the reference's sequencing previously alluded to in (v) and furthermore that "the obtained sequence was confirmed by semiautomated solid-phase Sanger sequencing" (Pg. 87, see figure 5).

With regard to claim 20, Ronaghi et al. teaches the above method wherein the detecting step (iii) measures the release of pyrophosphate(Page 85).

With regard to claim 21, Ronaghi et al further teach the method wherein the pyrophosphate release is detected by light emitted from a luciferin luciferase reaction(Fig. 1, Pg. 85).

With regard to claims 32, 33, and 34 Ronaghi et al. further teaches the method of claim 2 wherein step (iv), claim 4 wherein step (vi), and claim 19, wherein step (vii) is washing one or more reaction areas to remove excess of said deoxynucleotide or deoxynucleotide analogue in their teaching on the left side of page 85 of "washing of the immobilized DNA fragments between each nucleotide addition was performed" (Ronaghi pg. 85). Additionally the reference

Art Unit: 1634

teaches in the abstract that the "parallel processing of many samples in an automated manner is discussed".

With regard to claims 35-40 the reference anticipates the limitations of the method of claim 2, 35, 4, 19, 37, and 39 wherein the amount of DNA sample is in the range of about 1 femtomole to about 200 pmole and also about 0.1 pmol to about 200 pmol in their teaching on page 85 of "one picomole of the immobilized DNA fragment" being used in the sequencing reaction.

With regard to new claim 42, 43, 50 and 52 the reference anticipates the limitations of the method of claim 2 and claim 42 wherein said immobilized DNA is immobilized to a bead in their teaching on page 85 of "the biotinylated PCR products were immobilized onto streptavidincoated super paramagnetic beads Dynabeads M280-Streptavidin or M450-streptavidin" (left hand side), which were later used for sequencing.

But, with respect to Claims 4, 6, 12, 16, 19, 22-31, and new claims 41 and 43-56
Ronaghi et al. does not teach a method for identifying the sequence of a portion of sample DNA wherein the steps are performed in a microfluidic device that is a disk and the fluids are moved(claims 4, 12, 16, and 19) by centripetal force, such as that which is referred to on page 5, line 32 of the current specification. Additionally, they do not teach the microfluidic device comprising microchannel structures with a common application area and a reaction chamber in each of said microchannel structures. Furthermore, Ronaghi et al. does not teach labeling the deoxynucleotide, deoxynucleotide analogue, or dideoxynucleotide that is added in the method.

However, Mian et al. (US Patent 6,319,469 B1) teach performing the previously taught methods of Ronaghi inside another type of microfluidic device. Mian et al. teach performing the

Art Unit: 1634

steps of adding sample DNA on a reaction area in a microfluidic device(see Col. 49 lines 1-4), attaching or hybridizing single stranded DNA, and plainly adding sample DNA to a predetermined area on a microfluidic device that is a disc and whose fluids can be moved to various chambers(Col. 49 lines 2-19). Furthermore, the Mian et al. reference adds teachings of a disc-shaped, microfluidic device that causes fluid movement through the use of centripetal force(Col. 3 lines 5-25). The reference even further teaches that such methods and apparatus are advantageous as they fill the need in the art for a "simple, flexible, reliable, rapid, and economical microanalytic and microsynthetic reaction platform for performing biological, biochemical, and chemical analyses and syntheses that can move nanoliter to microliter amounts of fluids" (Col. 3 lines 5-10). The reference provides that the invention also advantageously combines "wet" chemistry capabilities with information processing, storing and manipulating ability. The addition of the disc-shaped microfluidic device that exploits centripetal force, to this method for sequence identification, conferred the ability to properly mix reaction components, remove reaction side products, and isolate desired reaction products and intermediates.(Col 3, lines 5-25)(Col 48, line 67) Furthermore, Mian et al. add the teaching of forming DNA to a "microchannel structure" within the microfluidic device. The reference teaches that; the unique disc shape and ability to move nanoliter to microliter amounts of fluid, including reagents and reactants, at rapid rates to effect the proper mixing of reaction components through the use of microchannel structures and centripetal force, provides a remedy for the many deficiencies of the status quo. The use of microchannels, functioning to separate micro-amounts of fluid reagents, and centripetal force, to move fluids into and out of reaction chambers, facilitates highthroughput analysis for both genome sequencing and routine clinical applications "that are

Art Unit: 1634

sophisticated(for professional, eg hospital, use), easy to use(for consumer eg at-home monitoring, uses), and portable (for field environmental testing, use)" (Col. 3 lines 19-22). In addition, with regard to the new limitations requiring multiple reaction areas containing immobilized DNA(i.e. new claims 45, 46, 48, 49, 54, and 56) Mian et al. teach "disks comprising a multiplicity of these synthetic arrays, permitting simultaneous synthesis of a plurality of dideoxynucleotide-terminated oligonucleotides" (Col. 49 lines 31-34). Furthermore, with regard to the new limitations requiring that the immobilized DNA is formed outside the microfluidic structure (i.e. claims 44 and 53) Mian et al. teaches in Col.42 lines 64-67 for example, that "in the practice of the method of the invention, the immobilized, labeled duplex is placed on the disk and subjected to a flow stream of a buffered solution contained on the disk" (Col. 42) also in Col. 43 lines 26-33 the reference teaches immobilization of DNA either before or after the DNA is on the disk.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have conducted the method of Ronaghi et al. in view of the methods of Mian et al. by incorporating a disc-shaped microfluidic device with microchannels and caused fluid flow through the use of centripetal force in order to have achieved the expected benefit of providing a method that could be used for the automation of larger sequencing projects and for the provision of a "high-throughput system."

With respect to Claims 6, 22, 25, 26, and 29-31 and the limitation of a fluorescently labeled dideoxynucleotide, Mian teaches a detection step that involves a labeled terminator (Col 49, lines 5-10). Mian et al. teach a method wherein the detection step comprises the DNA being transferred into a mixing chamber containing terminator solution by spinning the disk(Col. 47

Art Unit: 1634

lines 15, 28, 39 for example). Terminator solution typically comprises 100nl of a solution containing 5 picomoles of each deoxynucleotide and 0.5 picomoles of one dideoxynucleotide covalently linked to a fluorescent label. The set of dideoxynucleotide-terminated DNA fragments comprising the reaction mixture is then separated by capillary electrophoresis and the sequence of the fragments determined by laser-induced fluorescence detection. The reference further teaches that this mode of detection ie, discs comprising a multiplicity of these synthetic arrays with fluorescent labels, permits the simultaneous synthesis of a plurality of dideoxynucleotide-terminated oligonucleotides and therefore applicable in high throughput analysis of sequencing data or clinical approaches. Mian et al. teaches the use of a terminator solution containing a dideoxynucleotide covalently-linked to a fluorescent label in Example 7, Col. 49. In addition, Mian et al. teach, in addition to the aforementioned, fluorescently labeled dideoxynucleotide of Example 7, Example 3 which includes the incorporation of fluorescently labeled DNA to one or more reaction areas so that extension of primer occurs as a result from complementarity of the added dideoxynucleotides with the strand of sample DNA that is part of the immobilized double stranded DNA.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have conducted the method of Ronaghi et al. in view of the methods of Mian et al. and to have added a labeled terminator and fluorescently labeled dideoxynucleotides, in order to have achieved the benefit of providing a method that, would permit the simultaneous synthesis of a plurality of fluorescently labeled dideoxynucleotide-terminated oligonucleotides and therefore applicable in high throughput analysis of sequencing data or clinical approaches.

Response to Arguments:

Art Unit: 1634

Applicant's arguments filed 10/1/2004 have been fully considered but they are not persuasive. Applicant first reminds the examiner that section 103 requires consideration of the claimed invention "as a whole" and as such prevents evaluation of the invention part by part, in hindsight. However, the examiner maintains that the legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e., a reasonable expectation of obtaining similar properties. See , e.g. , In re O'Farrell , 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, there is express suggestion in the prior art that sequencing can be performed by many art-recognized methods. There is further evidence as shown in Ronaghi et al. that the method including detection of pyrophosphate release lends itself to the "possibility for parallel processing of many samples in an automated manner". This is sufficient for a reasonable expectation of success considering the Mian et al reference provides a parallel processing, automated, microfluidic device. The MPEP cites In re O'Farrell, which notes regarding "obvious to try" at page 1682, that,

"In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g., In re Geiger, 815 F.2d at 688, 2 USPQ2d at 1278; Novo Industri A/S v. Travenol Laboratories, Inc., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); In re Yates, 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); In re Antonie, 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention

Art Unit: 1634

or how to achieve it. In re Dow Chemical Co., 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1986), cert. denied, 107 S.Ct. 1606 (1987); In re Tomlinson; 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

The court in O'Farrell then, affirming the rejection, notes "Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art suggests varying a variety of parameters, since the prior art directly points to real time sequencing being performed in a microfluidic device in both the Ronaghi et al. reference and the Mian et al reference. This is also not a situation where only general guidance was given. The prior art provides specific guidance directing real time sequencing in a microfluidic device. It should further be noted that the new, independent claims as written do not require a particular method of sequencing to be used(i.e. do not require pyrosequencing.) and as a result the claims can be read broadly as long as the required elements of including a DNA polymerase and deoxynucleotide or deoxynucleotide analogue are met, which they are by both references. As a sequencing method is presently being defined by the claims, both references teach the same sequencing method and are appropriately combined in the obviousness rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally A Sakelaris whose telephone number is 571-272-0748. The examiner can normally be reached on M-Fri, 9-6:30 1st Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Art Unit: 1634

Page 15

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Sally Sakelaris

10/28/2004

JEFFREY FREDMAN PRIMARY EXAMINER

0/28/04